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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: F. Haviv, et al.

Serial No.: 09/703,233

Filed: October 31, 2000

For: N-ALKYLATED PEPTIDES HAVING ANTIANGIOGENIC ACTIVITY

Case No.: 6632.US.O2

Group Art Unit: 1653

Examiner: David. Lukton

Certificate of Mailing under 37 CFR §1.8(a):
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Commissioner for Patents
Washington, D.C. 20231

Date of Deposit: February 12, 2003

Jenny Rizzotto — 2/12/03 Date

TRANSMITTAL LETTER

The Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed herewith for the patent application identified above entitled, N-ALKYLATED PEPTIDES HAVING ANTIANGIOGENIC ACTIVITY, are the following:

1. Response to Restriction Requirement;
2. Extension of Time (37 CFR 1.136(a)); and
3. Return Receipt Postcard

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR 1.16, as well as any patent application processing fees under 37 CFR 1.17 associated with this communication for which full payment had not been tendered, to Deposit Account No. 01-0025.

Respectfully submitted,
F. Haviv et al.

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RESPONSE TO RESTRICTION REQUIREMENT
AND AMENDMENT A

Director of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

This communication is responsive to the Restriction Requirement dated September 30, 2002, having a period of response through February 28, 2003, pursuant to a four (4) month extension of time under 37 C.F.R. §§ 1.136(a).

Kindly enter this amendment and reconsider the application in view of the accompanying remarks.

Please replace claim 1 with the correspondingly numbered claim.

1 (Amended). A compound having a formula:

A1

$$\underset{1}{Xaa_1}\text{-}\underset{2}{Xaa_2}\text{-}\underset{3}{Xaa_3}\text{-}\underset{4}{Xaa_4}\text{-}\underset{5}{Xaa_5}\text{-}\underset{6}{Xaa_6}\text{-}\underset{7}{Xaa_7}\text{-}\underset{8}{Xaa_8}\text{-}\underset{9}{Xaa_9}\text{-}Xaa_{10}\text{-}Xaa_{11} \quad (I),$$

or a pharmaceutically acceptable salt thereof, wherein

at least one amide bond of an amino acid residue represented by Xaa_3, Xaa_4, Xaa_5,

Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is N-alkylated;

Xaa_1 is absent or Xaa_1 is selected from the group consisting of hydrogen, N-methylprolyl, and an acyl group, wherein the acyl group is selected from the group consisting of

R^1-$(CH_2)_n$-C(O)-, wherein n is an integer from 0 to 8 and R^1 is selected from the group consisting of N-acetylamino, alkoxy, alkyl, aryl, carboxy, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy; and

R^2-CH_2CH_2-O-$(CH_2CH_2O)_p$-CH_2-C(O)-, wherein p is an integer from 1 to 8 and R^2 is selected from the group consisting of hydrogen, N-acetylamino, and alkyl;

provided that Xaa_1 is absent only when Xaa_2 is N-(R^3)-prolyl;

Xaa_2 is an N-alkylated amino acid selected from the group consisting of N-(R^3)-alanyl, N-(R^3)-glycyl, N-(R^3)-norvalyl, and N-(R^3)-prolyl, wherein R^3 is C_1-C_5-alkyl; or Xaa_2 is an N-unalkylated amino acid selected from the group consisting of

β-alanyl,
D-alanyl,
4-aminobutyryl,
(1R,3S)-1-aminocyclopentane-3-carbonyl,
(1S,3R)-1-aminocyclopentane-3-carbonyl,
(1R,4S)-1-aminocyclopent-2-ene-4-carbonyl,
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,
asparaginyl,
3-(4-chlorophenyl)alanyl,
3-(4-cyanophenyl)alanyl,
glutaminyl,
glutamyl,
glycyl,
4-hydroxyprolyl,
3-(4-methylphenyl)alanyl,
prolyl,
seryl, and
threonyl;

Xaa_3 is an N-alkylated amino acid selected from the group consisting of N-(R^3)-alanyl, N-(R^3)-glycyl, N-(R^3)-leucyl, and N-(R^3)-phenylalanyl, wherein R^3 is as defined above; or Xaa_3 is an N-unalkylated amino acid selected from the group consisting of

alanyl,
(1S,3R)-1-aminocyclopentane-3-carbonyl,
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,
asparaginyl,
aspartyl,
3-(3-cyanophenyl)alanyl,
3-(4-cyanophenyl)alanyl,
glutaminyl,
glycyl,
leucyl,
lysyl(N-epsilon-acetyl),
3-(4-methylphenyl)alanyl,
norvalyl,
prolyl, and
phenylalanyl;

Xaa_4 is an N-alkylated amino acid selected from the group consisting of N-(R^3)-alanyl, N-(R^3)-glycyl, N-(R^3)-homophenylalanyl, N-(R^3)-isoleucyl, N-(R^3)-leucyl, N-(R^3)-norvalyl, N-(R^3)-phenylalanyl, N-(R^3)-D-phenylalanyl, N-(R^3)-seryl, N-(R^3)-tyrosyl, N-(R^3)-valyl, and N-(R^3)-D-valyl, wherein R^3 is as defined above; or Xaa_4 is an N-unalkylated amino acid selected from the group consisting of

alanyl,
alloisoleucyl,
allylglycyl,
2-aminobutyryl,
(1R,4S)-aminocyclopent-2-ene-4-carbonyl,
asparaginyl,
aspartyl,
3-[2-(5-bromothienyl)]alanyl,
3-(3-chlorophenyl)alanyl,
3-(4-chlorophenyl)alanyl,
3-(3-cyanophenyl)alanyl,

cyclohexylalanyl,
3-(3,4-dimethoxyphenyl)alanyl,
3-(3-fluorophenyl)alanyl,
3-(4-fluorophenyl)alanyl,
glutaminyl,
glycyl,
histidyl,
homophenylalanyl,
homoseryl,
isoleucyl,
leucyl,
lysyl(N-epsilon-acetyl),
methionyl,
methionyl(sulfone),
3-(4-methylphenyl)alanyl,
3-(naphth-1-yl)alanyl,
3-(naphth-2-yl)alanyl,
norornithyl,
norvalyl,
phenyalanyl,
phenylglycyl,
prolyl,
3-(3-pyridyl)alanyl,
3-(4-thiazolyl)alanyl,
3-(2-thienyl)alanyl,
seryl,
seryl(O-benzyl),
styrylalanyl,
tryptyl,
tyrosyl,
valyl, and
D-valyl;

Xaa_5 is an N-alkylated amino acid selected from the group consisting of N-(R^3)-D-homophenylalanyl, N-(R^3)-D-isoleucyl, N-(R^3)-D-leucyl, and N-(R^3)-D-phenylalanyl, wherein R^3 is as defined above; or Xaa_5 is an N-unalkylated amino

acid selected from the group consisting of

D-alanyl,
alloisoleucyl,
D-alloisoleucyl,
D-2-aminobutyryl,
D-3-(4-aminophenyl)alanyl,
D-asparaginyl,
D-3-(3-benzothienyl)alanyl,
D-*t*-butylglycyl,
D-(chlorophenyl)alanyl,
D-citrullyl,
D-3-(3-cyanophenyl)alanyl,
D-cyclohexylalanyl,
cyclohexylglycyl,
D-cysteinyl(S-acetamidomethyl),
D-cysteinyl(S-*t*-butyl),
D-3-(3,4-difluorophenyl)alanyl,
D-(3,4-dimethoxyphenyl)alanyl,
D-glutaminyl,
glycyl,
D-homophenylalanyl,
D-homoseryl,
isoleucyl,
D-isoleucyl,
D-leucyl,
D-lysyl(N-epsilon-nicotinyl),
D-lysyl,
D-methionyl,
D-3-(4-methylphenyl)alanyl,
D-3-(naphth-1-yl)alanyl,
D-3-(naphth-2-yl)alanyl,
D-3-(4-nitrophenyl)alanyl,
D-norleucyl,
D-ornithyl,
D-penicillaminyl(S-acetamidomethyl),
D-penicillaminyl(S-benzyl),

D-penicillaminyl(S-methyl),
D-penicillaminyl,
D-3-(pentafluorophenyl)alanyl,
D-phenylalanyl,
D-prolyl,
D-seryl(O-benzyl),
D-seryl,
D-(2-thienyl)alanyl,
D-threonyl(O-benzyl),
D-threonyl,
D-3-(3-trifluoromethylphenyl)alanyl,
D-(3,4,5-trifluorophenyl)alanyl,
D-tryptyl,
D-tyrosyl(O-ethyl),
D-tyrosyl, and
D-valyl;

Xaa_6 is an N-alkylated amino acid selected from the group consisting of N-(R^3)-aspartyl, N-(R^3)-glutamyl, N-(R^3)-glycyl, N-(R^3)-seryl, N-(R^3)-threonyl, N-(R^3)-threonyl(O-benzyl), and N-(R^3)-tyrosyl, wherein R^3 is as defined above; or Xaa_6 is an N-unalkylated amino acid selected from the group consisting of

alanyl,
allothreonyl,
D-allothreonyl,
allylglycyl,
asparaginyl,
aspartyl,
glutaminyl,
glycyl,
histidyl,
homoseryl,
D-homoseryl,
3-(4-hydroxymethylphenyl)alanyl,
isoleucyl,
lysyl(N-epsilon-acetyl),
methionyl,

3-(naphth-2-yl)alanyl,
norvalyl,
octylglycyl,
prolyl,
3-(3-pyridyl)alanyl,
seryl,
D-seryl,
threonyl,
D-threonyl,
tryptyl,
tyrosyl, and
tyrosyl(O-methyl);

Xaa_7 is an N-alkylated amino acid selected from the group consisting of N-(R^3)-alanyl, N-(R^3)-glycyl, N-(R^3)-isoleucyl, N-(R^3)-leucyl, N-(R^3)-D-leucyl, N-(R^3)-norleucyl, N-(R^3)-norvalyl, N-(R^3)-seryl, N-(R^3)-threonyl, and N-(R^3)-valyl, wherein R^3 is as defined above; or Xaa_7 is an N-unalkylated amino acid selected from the group consisting of

alanyl,
allothreonyl,
allylglycyl,
3-(4-amidophenyl)alanyl,
2-aminobutyryl,
arginyl,
asparaginyl,
cyclohexylalanyl,
glutaminyl,
D-glutaminyl,
glycyl,
homoalanyl,
homoseryl,
4-hydroxyprolyl,
leucyl,
D-leucyl,
lysyl(N-epsilon-acetyl),
methionyl sulfone,

methionyl sulfoxide,
methionyl,
norleucyl,
norvalyl,
D-norvalyl,
octylglycyl,
ornithyl(N-delta-acetyl),
phenylalanyl,
propargylglycyl,
seryl,
D-seryl,
threonyl,
tryptyl,
tyrosyl, and
valyl;

A1

Xaa_8 is an N-alkylated amino acid selected from the group consisting of N-(R^3)-alanyl, N-(R^3)-D-alanyl, N-(R^3)-isoleucyl, and N-(R^3)-leucyl, wherein R^3 is as defined above; or Xaa_8 is an N-unalkylated amino acid selected from the group consisting of

alanyl,
alloisoleucyl,
D-alloisoleucyl,
allylglycyl,
citrullyl,
glycyl,
isoleucyl,
D-isoleucyl,
leucyl,
D-leucyl,
lysyl(N-epsilon-acetyl),
D-lysyl(N-epsilon-acetyl),
methionyl,
3-(naphth-1-yl)alanyl,
norvalyl,
prolyl,

D-prolyl, and
valyl;

Xaa_9 is the N-alkylated amino acid N-(R^3)-arginyl, wherein R^3 is as defined above; or Xaa_9 is an N-unalkylated amino acid selected from the group consisting of

[(4-amino-N-isopropyl)cyclohexyl]alanyl,
3-(4-amino-N-isopropylphenyl)alanyl,
arginyl($N^G N^{G'}$diethyl),
arginyl,
D-arginyl,
citrullyl,
glutaminyl,
3-(4-guanidinophenyl)alanyl,
histidyl,
homoarginyl,
lysyl(N-epsilon-isopropyl),
lysyl(N-epsilon-nicotinyl),
lysyl,
norarginyl,
ornithyl,
ornithyl[N-delta-(2-imidazolinyl)],
ornithyl(N-delta-isopropyl), and
3-(3-pyridyl)alanyl;

Xaa_{10} is an N-alkylated amino acid selected from the group consisting of N-(R^3)-alanyl, N-(R^3)-D-alanyl, N-(R^3)-glycyl, N-(R^3)-homoalanyl, and N-(R^3)-norvalyl, wherein R^3 is as defined above; or Xaa_{10} is an N-unalkylated amino acid selected from the group consisting of

D-alanyl,
2-aminobutyryl,
D-2-aminobutyryl,
2-aminoisobutyryl,
3,4-dehydroprolyl,
4-hydroxyprolyl,
phenylalanyl,
prolyl,

D-prolyl,
1,2,3,4-tetrahydroisoquinoline-3-carbonyl, and
D-valyl; and

Xaa_{11} is a hydroxy group or an amino acid amide selected from the group consisting of:

alanylamide,
D-alanylamide,
alanylethylamide,
D-alanylethylamide,
azaglycylamide,
glycylamide,
glycylethylamide,
lysyl(N-epsilon-acetyl),
D-lysyl(N-epsilon-acetyl),
N-methyl-D-alanylamide,
sarcosylamide,
serylamide,
D-serylamide,
a residue represented by the formula

$$-NH-(CH_2)_s-\underset{\displaystyle R^4}{\overset{\displaystyle |}{C}}HR^5$$

, and
a group represented by the formula $-NH-R^6$; wherein
s is an integer from 0 to 8;
R^4 is selected from the group consisting of hydrogen, alkyl, and a 5- to 6-membered cycloalkyl ring;
R^5 is selected from the group consisting of hydrogen, alkoxy, alkyl, aryl, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy;
provided that s is not zero when R^5 is hydroxy or alkoxy; and
R^6 is selected from hydrogen and hydroxy.